PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT : HELM ET AL.

SERIAL NO. : 09/133,766

FILED : AUGUST 12, 1998

TITLE : ALLERGEN/INFLAMMATORY TESTING AND DIAGNOSIS

EXAMINER : RON SCHWADRON, PH.D.

ART UNIT : 1644

#10 Ext. of Time (2nd) Proposed & Req. for Interview Encl 08/24/00

REPLY TO THE FIRST OFFICE ACTION

Honorable Commissioner for Patents
and Trademarks
Washington, D.C. 20231

Dear Sir:

In response to the Office Action dated Mach 17, 2000, reconsideration and withdrawal of the rejection is respectfully requested in view of the following remarks.

The 103 rejection of the claims and, in particular, the Examiner's rejection of Claims 17 and 33 as being obvious over Wilson et al. and Claims 16-24, 32, and 33 as being obvious over Cantor et al., Gilfillan et al., Levi-Schaffer et al., and Bochner et al. is respectfully traversed.

The respective prior art teachings of Cantor et al, Gilfillan et al, Levi-Schaffer et al and Bochner et al can be illustrated figuratively, for example, as shown in the attached Annexes - Schemes P, adapted from Molecular Biology of the Cell, Alberts et al, 2nd ed., Garland Publishing NY 1989, in which symbols have the meaning as shown. This can be more easily compared with the method of the invention which is illustrated figuratively for example as shown in the attached Annex - Scheme I, which uses the same notation as that of the prior art Schemes P; clearer drawings will be provided shortly.

The Examiner has taken the position that it would have been obvious to the skilled person to have created the method of the invention because Wilson et al teaches that sensitized transfected RBL clones support the release of mast cell mediators ... upon challenge with allergen antigen.

With reference to Schemes P (Wilson) and Scheme I, important differences are apparent in the sequence of steps employed, the sequence of response and the usefulness of the inferences drawn. Wilson concludes that in situ assays of individuals may be developed using this marker response as a tool

in place of mediator release and thereby avoiding creating an allergic response in the individual.

The Examiner also relies on the disclosure in Levi-Schaffer et al, at p.308, that mast cells respond to IgE dependent or IgE independent activators, indicating that this would lead a routineer to use the prior art methods in the absence of a sensitizing agent to screen for allergenicity of a substance simply because "Levi-Schaffer et al teach that mast cell activation results in the release of mediators that cause the signs and symptoms of the allergic response and that mast cells respond to IgE independent factors, and that Bochner et al teach that allergens that stimulate the release of mediators from mast cells/basophils in an IgE independent manner were known in the art, and therefore that the antigen which causes mast cell activation is an allergen".

With reference to Scheme P (Levi-Schaffer), Scheme P (Bochner) and Scheme I, important differences are once again apparent in the sequence of steps employed, the sequence of response and the usefulness of the inferences drawn. No comment or inference is made in Levi-Schaffer as to the mechanism, role or

usefulness of IgE independent release. In fact, Levi-Schaffer concludes that long term human mast cell cultures are desirable to assess in a human system what has been shown in a transfected rodent system, this creates a prejudice away from (i.e., teaches against) the present invention.

As previously submitted, the present invention employs techniques known in the art, as illustrated in the cited documents, including the technique of using transfected rodent mast cells to model human cells, and the technique of exposing cell lines to allergen and detecting a response in the form of mediator release. The enclosed Schemes which are pictorial representations of the cited documents use notation taught in common general knowledge, specifically in fundamental textbook teaching of the subject of immunology, including antibody binding, mediator release, class switching of cell types to synthesize substances which are involved in the allergic reaction and the like. It should be apparent that the applicant does not intend to claim these known techniques and common general knowledge as their invention.

In fact, it will be clear that the teaching of immunology relates to observing responses and monitoring the substances

involved, to determine the underlying bimolecular mechanisms of an individual. The present invention could in fact be said to derive from the teaching of environmental chemistry and relates to observing allergic responses and monitoring the substances involved, to determine the chemical properties of natural and synthetic substances. Immunology uses substances as a tool to study cell response, and environmental chemistry uses cell lines as a tool to study chemical properties.

The Examiner has observed that the various prior art documents vary in their use of sensitized or unsensitized clones which may be derived from human or transfected rat cell lines to study IgE dependent or independent release of mediators. While these factors are all significant in the results obtained they are not fundamental to the invention and the Examiner should not be distracted by overemphasizing their significance. It is important to note that Levi-Schaffer teaches that observations from rat cell lines can only be used as a suggestion of possible release mechanisms in human cell lines. This would be a disincentive to the routineer to develop an assay based on these systems or at best to be an incentive to the routineer that the use of the rodent cell lines relates to the study of individual human responses.

The present invention is illustrated by Scheme I attached. The invention results from two distinct departures being made from the prior art.

Firstly, from the scheme it is apparent that the important step of departing from the mainstream teaching of the prior art (Wilson et al, Gilfillan et al) by failing to sensitize transfected rat mast cells (or basophil or T-helper cells), takes advantage of the known (Levi-Schaffer) IgE independent production of IL-4 which induces the known class switching to IgE synthesizing cells which are capable of generating mediator and marker release of the type previously observed in the presence of IgE, by Cantor et al, Gilfillan et al, Levi-Schaffer et al and Bochner et al. Levi-Schaffer observed the release of histamine in the presence of different interleukins, to assess whether inhibition of histamine could be addressed by this mechanism, but failed to pursue the significance of the IgE independence. The invention derived from the realization that a common principle underlies allergic responses and suggests that it is possible to predict allergenicity by means of a biological assay system, since any substance which induces cells to synthesis and secrete IL-4 which is involved in the allergic response must be potentially allergenic. It could not

therefore have been said to be obvious either to alter the conditions of the in vitro prior art to attempt to elicit a response previously observed in vivo (IgE independent response) for different reason and under different conditions (absence of IgE).

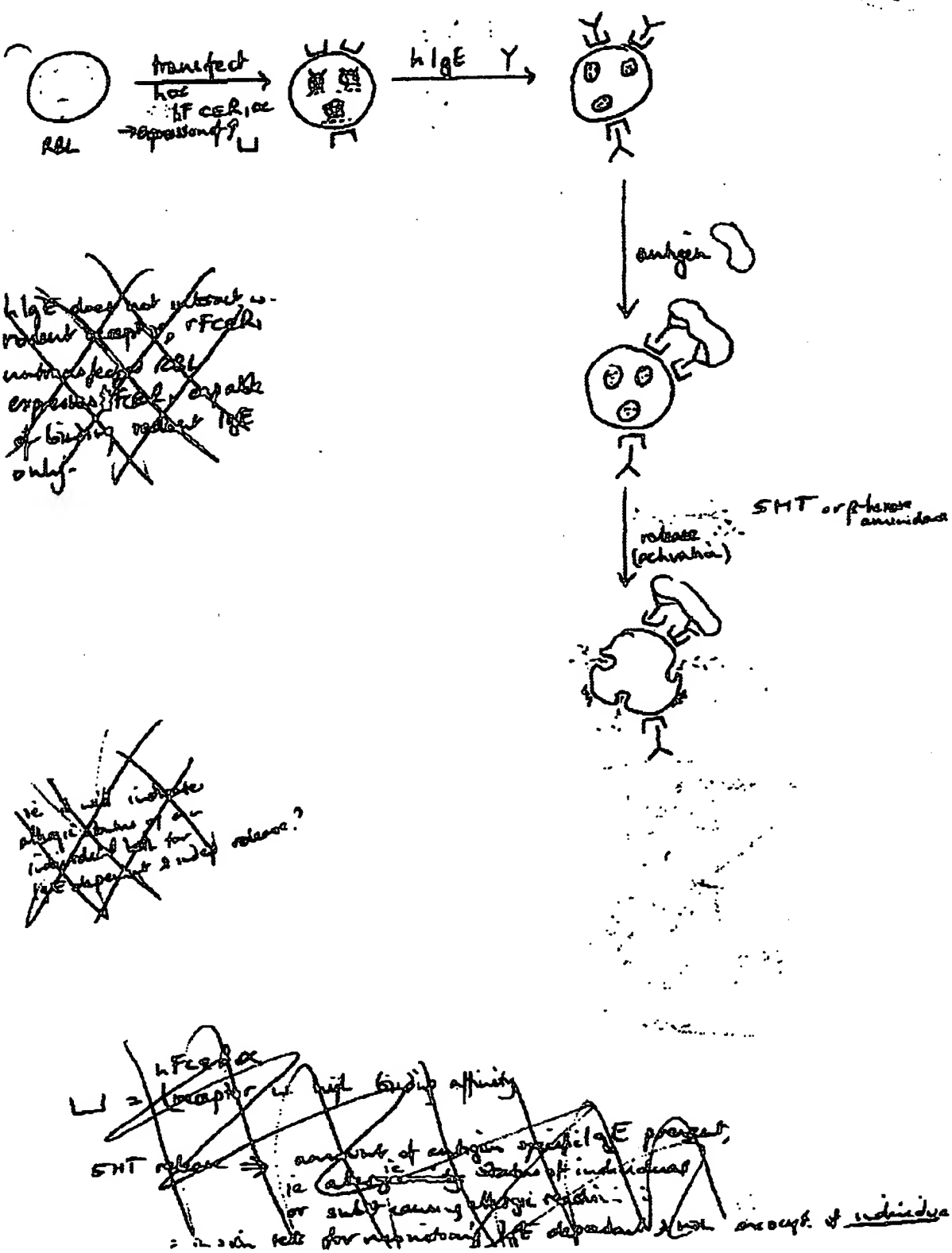
Secondly, the further important step of departing from the prior art (Levi-Schaffer et al) by looking for IgE independent release from transfected mast cells leads to a utility for the claimed invention. The observations of Levi-Schaffer et al and Bochner et al do not disclose or suggest any utility for IgE independent mediator release. The method of the invention however leads to the development of an assay which can, for the first time, be used to determine whether any substance, known or unknown, has the capacity to elicit an allergic response from any individual, independent of sensitization, on single or repeat dosing, in high or low levels etc.

Applicant's submit that a distinction must be made between an IgE independent mechanism taking place in presence of IgE, i.e., as a study or an individual, and an IgE independent mechanism taking place in the absence of IgE, i.e., as a study or a chemical substance. It is with this distinction in mind that

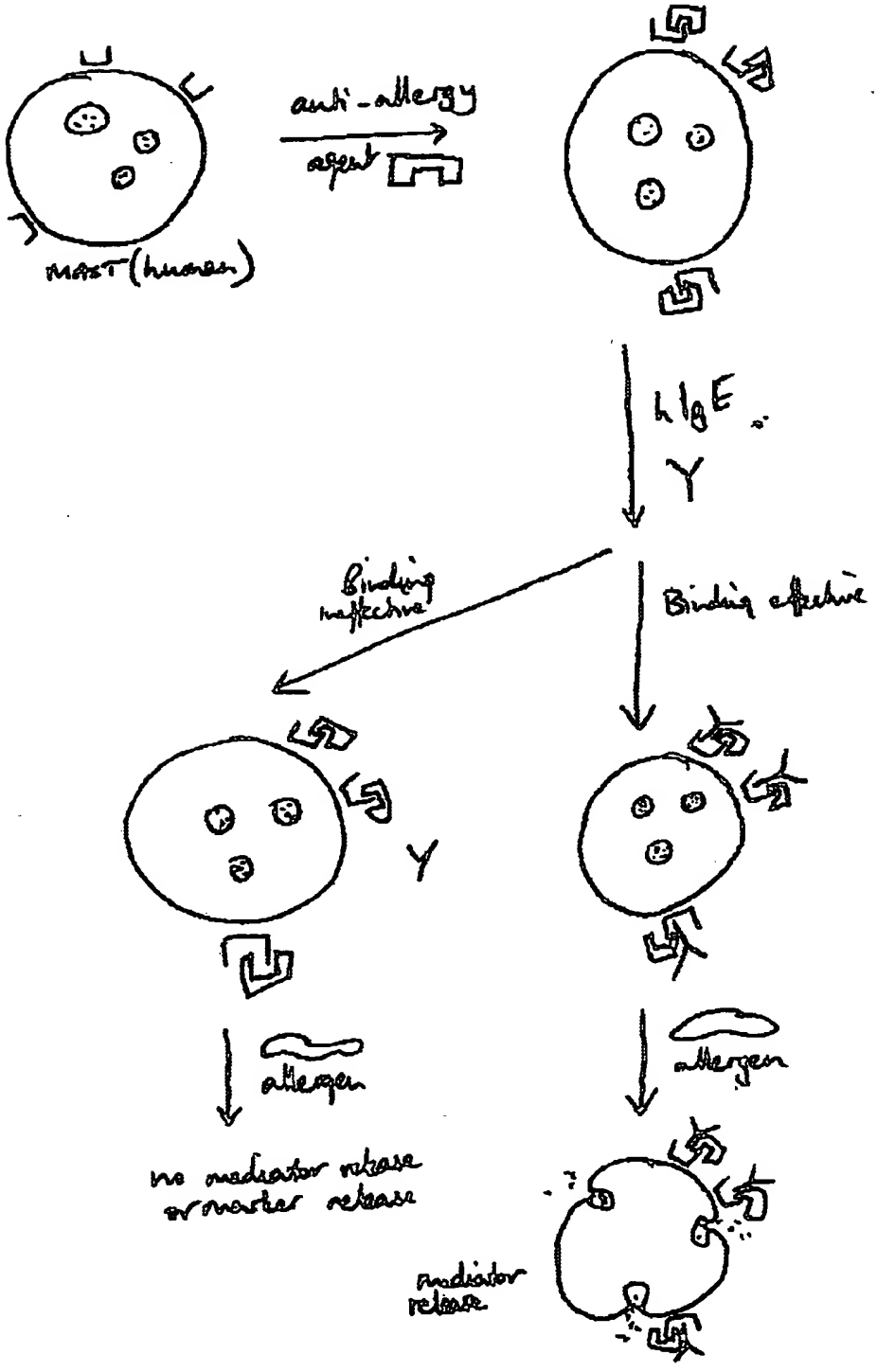
Applicants' submit that the Examiner is viewing the claimed invention with hindsight, which is of course, patently improper.

In view of the foregoing, and with reference to the previously submitted Declaration, which reviews the further work which has been initiated directly by the present invention and illustrates for the benefit of the Examiner the huge significance of the novel method claimed, it is respectfully submitted that the claims are patentably distinguishable over the references of record. The implications on regulating additives of food, paints, textiles, detergents and innumerable other product type which may be brought to the market unaware of the effect which they may potentially have on an individual are enormous, to the extent that the assay of the invention could become a standard screen for any diligent new product developer. With this significance in mind, it cannot be said that the invention is obvious over the prior art which has observed a phenomenon underlying the invention but has failed to grasp its significance. Accordingly, it is believed that the claims are patentable over each of the cited references.

SCHEME P1 (WILSON)

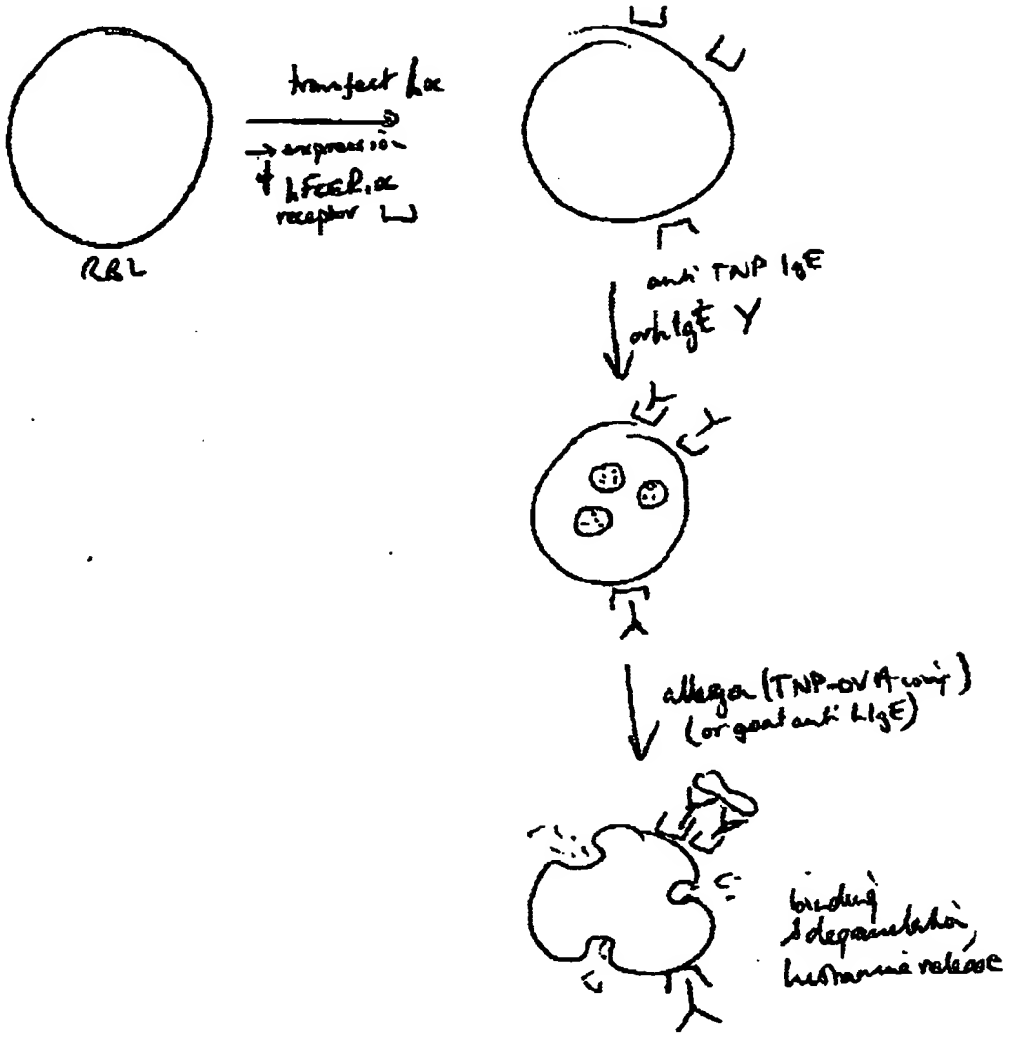


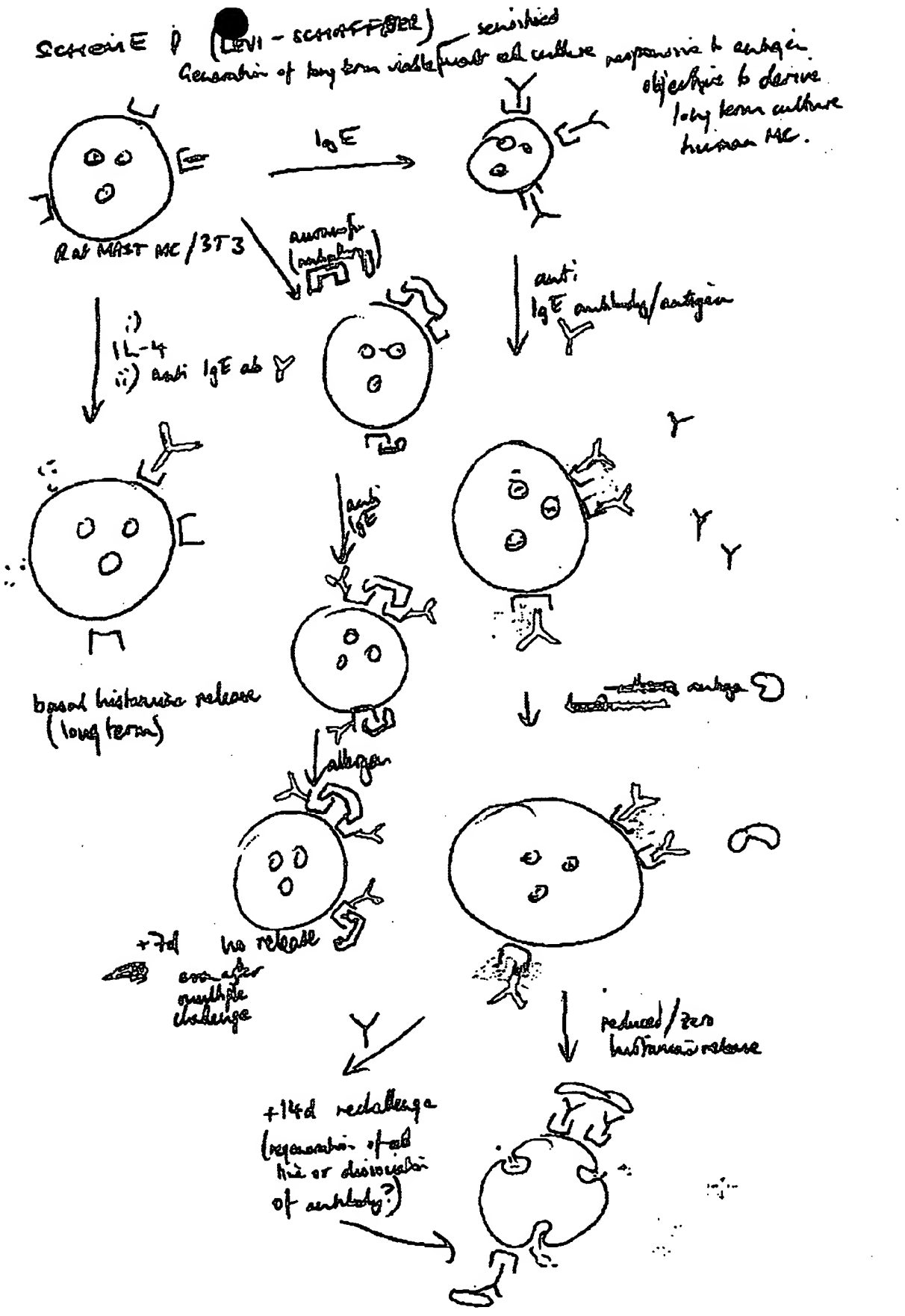
SCHEME P (CANTOR)



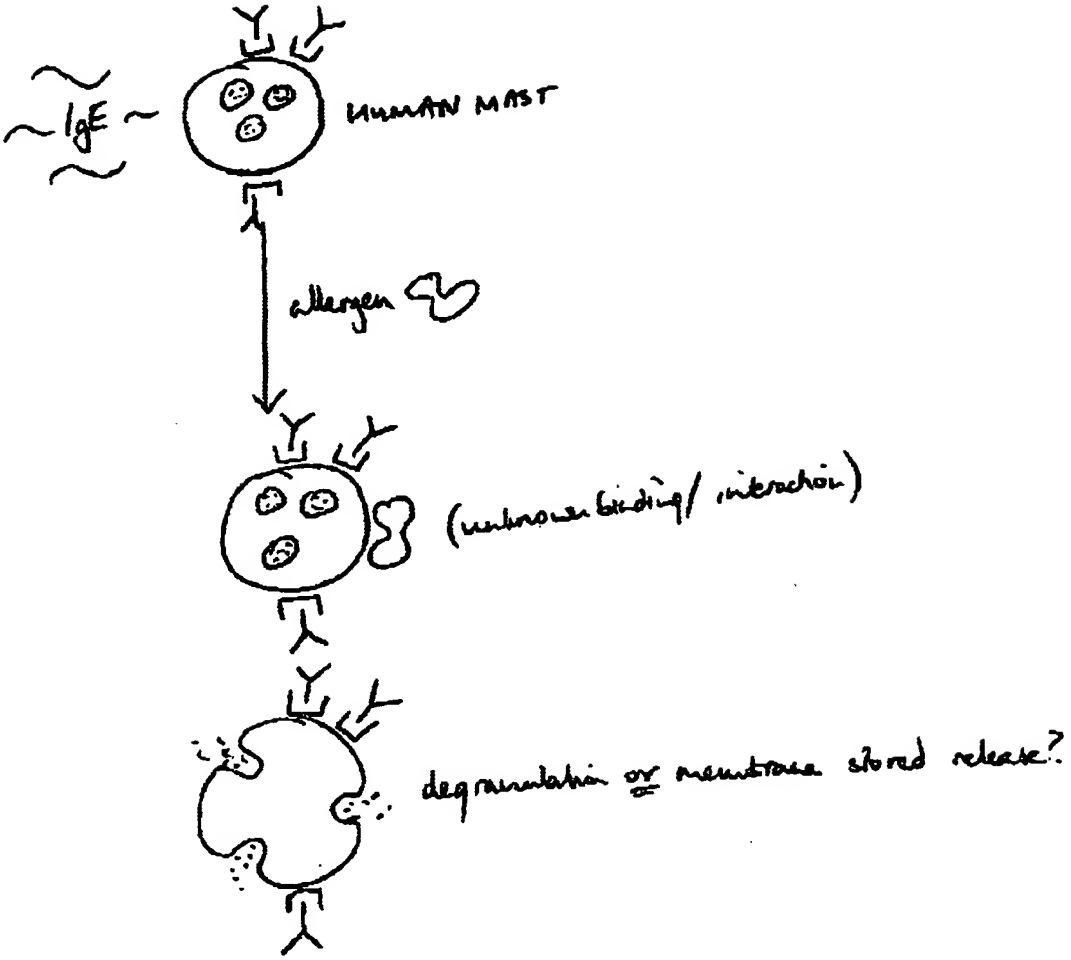
P (GILFILLAN)

Establish RAT RBL cell lines transfected w. hFcεRIα which can be challenged w. allergen & release histamine

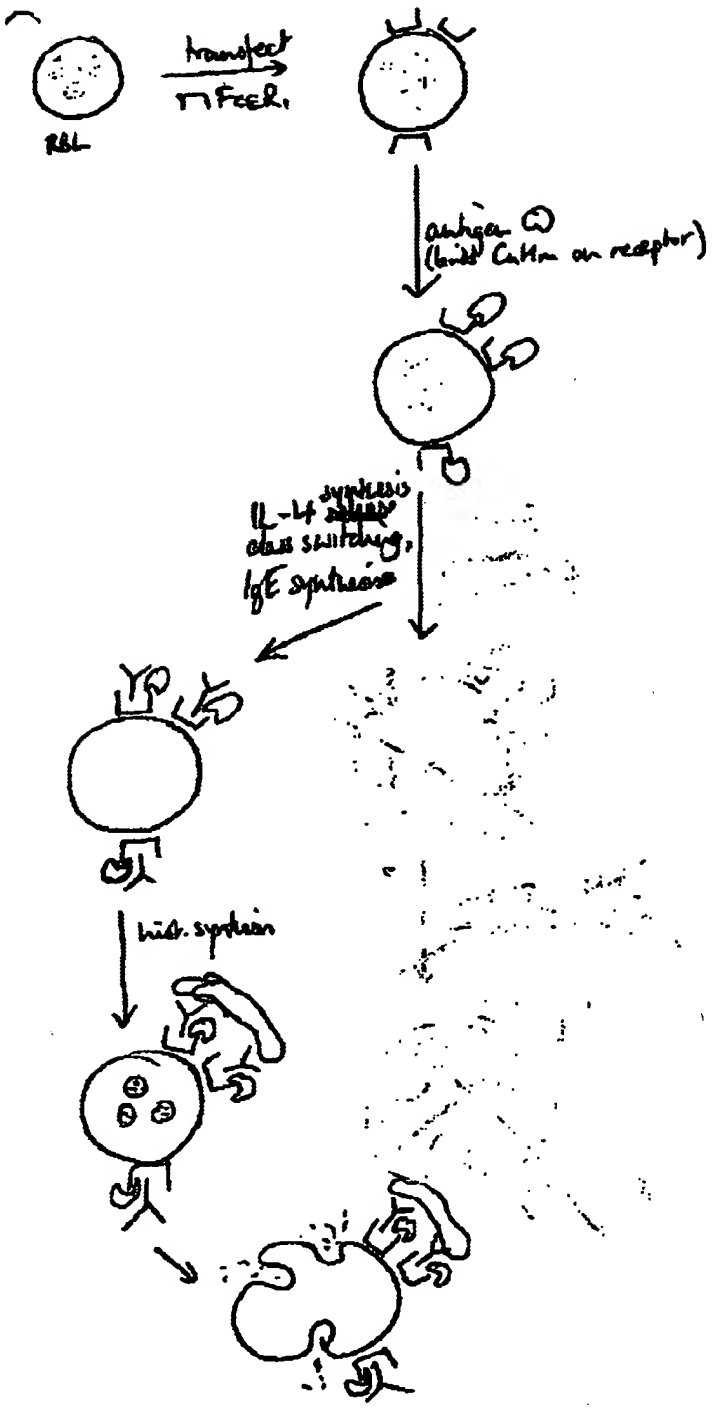



SCHEME I (LEVI - SCHAFFER)
sensitized
Generation of long term viable/functional cell culture responsive to antigen
objective to derive long term culture human MC.
IgE
Rat MAST MC/3T3
anti-IgE (rabbit)
anti IgE antibody/antigen
i) IL-4
ii) anti IgE ab
anti IgE
basal histamine release (long term)
antigen
allergen
+7d
no release even after multiple challenge
reduced/zero histamine release
+14d rechallenge (regeneration of cell line or desensitization of antibody?)

SCHEME P (BOCHNER)



Scheme I


transfect
FcεR1
RBL
antigen
(binds CaMm on receptor)
IL-4 synthesis
class switching,
IgE synthesis
IgE synthesis

MOLECULAR BIOLOGY OF THE CELL

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